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Title Page

Title: Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) – Diagnostic pitfalls and treatment approach

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Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by progressive weakness and sensory loss, often affecting patients' ability to walk and perform activities of daily living independently. With the lack of a diagnostic biomarker, the diagnosis relies on clinical suspicion, clinical findings, and the demonstration of demyelinating changes on electrodiagnostic testing and nerve pathology. As a result, patients can often be misdiagnosed with CIDP and unnecessarily treated with immunotherapy. Interpreting the electrodiagnostic testing and cerebrospinal fluid (CSF) findings in light of the clinical phenotype, recognizing atypical forms of CIDP, and screening for CIDP mimickers are the mainstays of the approach to patients suspected of having CIDP, and are detailed in this review. We also review the currently available treatment options including intravenous immunoglobulin, corticosteroids and plasma exchange, and discuss how to approach treatment-refractory cases. Finally, we emphasize the need to adopt objective outcome measures to monitor treatment response.

Keywords

CIDP, IVIG, Steroids, Plasma exchange, Diagnosis, Treatment

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune disorder of peripheral nerve and nerve root function, typically presenting with proximal and distal symmetrical weakness, areflexia, and disease progression that continues beyond 8 weeks.[1] The condition was first described and named by Peter J. Dyck in 1975.[2] The clinical features are predominantly those of large myelinated fiber involvement producing muscle weakness and sensory ataxia. The annual incidence is estimated to be around 1 per 100,000 persons; prevalence figures vary greatly, from 3-9 cases per 100,000 population, depending on diagnostic criteria and patient ascertainment techniques used.[3-5]

CIDP is caused by macrophage-mediated inflammatory demyelination involving proximal greater than distal nerve segments. Inflammatory infiltrates are adjacent to myelinated fibers or perivascularly in the epineurium (**Figure 1**). Early in the disease course, segmental demyelination predominates (best seen on teased nerve fiber preparations), but with time and ongoing demyelination, there is development of onion-bulbs (stacks of Schwann cell processes)

that accrue in abortive remyelination attempts, producing hypertrophic nerves.[2] The onion-bulbs in CIDP often occur in a 'mixed pattern' (**Figure 2**) because patchy inflammatory demyelination produces myelinated nerves surrounded by large onion bulbs adjacent to normal myelinated fibers.[6] This unequal demyelination explains the electrodiagnostic (EDX) findings of temporal dispersion typically found in CIDP. Immune mechanisms, involving such pathways as macrophage-mediated expression of co-stimulatory molecules B7-1 and B7-2, are directed towards Schwann cells and myelin epitopes, although the exact immune targets are unknown.[7] The emergence of specific antibodies, namely neurofascin-155 and contactin-1, points to nodal- or para-nodal specific pathology in a subset of patients.[8] However, these cases respond differently to treatment. Treatment-wise, intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin (SCIG), corticosteroids (CCS), and plasma exchange (PE) all show benefit in classical CIDP, albeit each with limitations.

The diagnosis of CIDP remains clinical, supported by EDX studies. In this review, we address the diagnostic pitfalls of CIDP and provide a practical approach to its evaluation. We then discuss currently available treatments and our own treatment approach.

The phenomenon of CIDP misdiagnosis and overtreatment

Despite established diagnostic criteria, best set out in the European Federation of Neurologic Societies / Peripheral Nerve Society (EFNS/PNS) criteria,[9] and well-recognized clinical characteristics of typical CIDP, misdiagnosis is not uncommon and immunotherapy

unnecessarily administered. This misdiagnosis of other neuropathies as CIDP is best described in a study by Allen et al. in which 47 percent of 59 patients referred for a putative diagnosis of CIDP did not eventually meet the clinical and EDX criteria for CIDP.[10] The authors found that the diagnostic error is mostly due to the over-reliance on mild nerve conduction abnormalities falsely interpreted as demyelination, insignificant elevation of cerebrospinal fluid (CSF) protein, or self-reported rather than objective improvement with therapy.

With regards to EDX testing, findings that are commonly misinterpreted as suggesting CIDP include amplitude-dependent slowing in length-dependent neuropathies, amplitude-independent slowing in diabetic polyneuropathies, isolated distal latency changes in the fibular nerve (when recording over the extensor digitorum brevis), and focal slowing across common entrapment sites.[11] Thus, it is important to interpret the EDX findings in light of the clinical phenotype of a particular patient, and to consider alternative etiologies when patients display atypical clinical features, unusual laboratory findings, and no objective evidence of response to treatment.

Another issue of importance is that of over-treatment of CIDP even when the diagnosis is correct. This may occur in situations where physicians do not vigorously wean treatment, when patients become psychologically reliant on treatment (even if not indicated), and in chronic cases of CIDP with secondary axonal loss, wherein immunotherapy may not be effective.[12,13]

Clinical features of typical CIDP

The classical CIDP phenotype is a symmetrical, sensory and motor polyradiculoneuropathy, with combined proximal and distal weakness, with areflexia, and without much associated pain. Chronic refers to progression beyond 8 weeks. Distal motor deficits are usually more pronounced and the sensory deficits are large-fiber predominant. The reason for this is that the fibers with the most myelin are most severely involved pathologically. Any clinical presentation that deviates from this picture should prompt consideration for alternative etiologies or an atypical form of CIDP **(Table 1)**. A pure large fiber sensory neuropathy with ataxia should lead to consideration for disease mimickers, separate entities altogether, or the CIDP variant termed chronic immune sensory polyneuropathy (CISP).[14] In addition, multifocal, asymmetric, and upper limb predominant disease should prompt consideration for multifocal CIDP.[15] Furthermore, typical CIDP patients do not usually have associated systemic symptoms such as fever, malaise, severe pain, or dysautonomia.[16]

Electrodiagnostic features and ancillary testing

As alluded to earlier, clinical features should be considered first and foremost as part of good clinical practice prior to interpreting EDX findings. Validated demyelinating criteria such as the EFNS/PNS criteria should be used to determine if the EDX findings are truly demyelinating. However, detecting demyelination may be limited by "the ceiling effect" of EDX

testing, where sensory and motor responses may be low or absent in electrophysiologically advanced cases. This can be due to secondary axonal loss, temporal dispersion, or conduction block. Furthermore, when demyelination is confined to the nerve roots, patients may have no clear demyelinating features on EDX testing, especially when F-waves are absent. In these cases, needle EMG is essential. A predominantly demyelinating process (conduction block or temporal dispersion) should be suspected when the changes on needle EMG are unexpectedly mild (reduced recruitment with only mildly enlarged motor unit potentials and only scarce abnormal spontaneous activity), even in the presence of low amplitude motor responses. Lastly, it is worth noting that other demyelinating neuropathies may fulfill EDX criteria for CIDP, but have distinctive clinical and laboratory features.

CSF protein elevation is not mandatory for many CIDP experts, but is a supportive laboratory finding present in more than 90% of CIDP patients.[17] However, it is nonspecific, as it is influenced by age and other comorbid conditions such as diabetes mellitus and degenerative spinal stenosis.[18] Raising the upper reference limit for CSF protein to greater than 45mg/dl increases its specificity in diagnosing CIDP without compromising its sensitivity (specifically using cutoffs of 50 mg/dl for patients <50 years and 60 mg/dl for patients ≥50 years).[19] MRI and ultrasound findings are not a major focus of this review, although nerve root thickening and plexus enlargement on MRI[20] as well as proximal median nerve and brachial plexus enlargement on ultrasound,[21,22] respectively, may be helpful in the diagnostic workup.

Nerve biopsy is not needed when the presentation is one of typical CIDP. However, nerve biopsy should be considered in rapidly progressive or treatment-refractory neuropathy, in multifocal cases, or when vasculitis, amyloidosis, or a neoplastic process are suspected.

Patterns suggestive of atypical CIDP or disease mimickers

In the following section, we discuss clinical patterns and findings that should alert the healthcare provider to atypical CIDP subtypes or disease mimickers (**Table 1**).

1. Rapid clinical progression By definition, CIDP is a chronic disease that progresses beyond 8 weeks. A slowly progressive course is more common in adults, whereas a relapsing and remitting course is more common in children.[23] If symptoms reach nadir within 4 weeks from onset, then Guillain Barre Syndrome (GBS) should be considered. Patients with treated GBS may also experience treatment-related fluctuation, which needs to be distinguished from CIDP.[24] Adding to the diagnostic challenge is the entity of acute-onset CIDP (A-CIDP), in which patients present acutely but continue to progress beyond 4-8 weeks, and which is further defined as > 3 relapses after 9 weeks.[24] A-CIDP is not phenotypically an 'atypical' form of CIDP (as far at the clinical and electrodiagnostic features), but is atypical in its clinical course, with an unusually rapid onset. The challenge is to recognize it early and differentiate it from GBS, as A-CIDP will need ongoing immunotherapy. Certain features suggest A-CIDP as opposed to GBS. A-CIDP patients are less severely affected, do not need mechanical ventilation, rarely have cranial nerve involvement, and have more typical CIDP demyelinating findings on EDX, when

compared to those with GBS. Less commonly, patients may follow a monophasic course and reach nadir in 4-8 weeks, a separate entity called subacute inflammatory demyelinating polyneuropathy (SIDP).[25,26] In patients presenting with subacute onset neuropathy with coarse tremor, ataxia, and distal weakness, testing for the CIDP nodopathy subtypes should be pursued, particularly neurofascin-155 and/or contactin-1 antibodies.[27] Nodopathies represent variants of typical CIDP in which proteins near or at the node of Ranvier are targeted by IgG4 antibodies, and constitute a sizeable minority of CIDP patients.[28] Finally, apparent worsening in CIDP may occur because the effect of treatment wears off; this wearing-off effect may be mislabeled as treatment-refractory CIDP.[29]

2. Length-dependent sensory greater than motor, axonal-predominant peripheral neuropathy. Length-dependent sensory predominant peripheral neuropathy can be due to many causes, and is often misdiagnosed as CIDP because of non-specific EDX abnormalities interpreted as demyelinating. This phenotype is similar to the mild slowing of conduction velocities seen in length-dependent diabetic polyneuropathy.

3. Non length-dependent sensory ganglionopathy/neuronopathy When there is a marked ataxic component with prominent large fiber involvement at onset, a sensory ganglionopathy might be considered. Two causes of sensory ganglionopathy are paraneoplastic ganglionopathy and Sjögren's syndrome. In addition, the sensory variant of CIDP - CISP - should be considered.[14,30] Although EDX studies are normal in CISP, somatosensory latencies are prolonged, CSF protein is elevated, and lumbar rootlet biopsies show loss of large myelinated

nerve fibers, onion-bulb formation (evidence of ongoing demyelination and remyelination) and endoneurial macrophages.[14]

4. Upper-limb-predominant neuropathy Multifocal CIDP (multifocal asymmetric demyelinating sensory and motor neuropathy [MADSAM] or Lewis Sumner Syndrome), as well as multifocal motor neuropathy (MMN) should be considered in the setting of asymmetric onset upper limb neuropathy. Here, the weakness is asymmetric, patchy, and disproportionately distal, in contrast to typical CIDP, which is symmetrical. In axonal, upper-limb-predominant neuropathy, a motor neuron disease should be considered, especially when there is marked atrophy and asymmetry. When associated with troublesome pain, an inflammatory brachial plexus neuropathy (neuralgic amyotrophy or Parsonage Turner syndrome), or vasculitis should be considered.

The EDX demyelinating features found in multifocal CIDP include slowing of conduction velocities, prolongation of F-waves and distal latencies, temporal dispersion and conduction block; this stands in contrast to MMN, where the main "demyelinating" feature is motor conduction block. The pathology of multifocal CIDP is inflammatory demyelination, similar to classical CIDP, and stands in contrast to the pathology of MMN, which involves axonal degeneration and unequal loss of myelinated nerve fibers.[31] In motor neuron disease, EDX findings may show slightly slowed motor velocities, but markedly reduced compound muscle action potential amplitudes, as well as dense fibrillation potentials on needle EMG.

5. Sensory and motor demyelinating neuropathy. The main two entities under this category are hereditary motor and sensory demyelinating neuropathy or Charcot Marie Tooth disease type 1 (CMT1) and paraproteinemic neuropathy. CMT1 usually presents with a much slower progression. On clinical examination, the sensory and motor deficits are predominantly distal and associated with pes cavus and hammer toes, often with positive family history. On EDX testing, the demyelination most often consists of uniform slowing with no conduction block or temporal dispersion and the F-wave latencies are not prolonged in comparison to the F-wave estimates.[32] Furthermore, on nerve biopsy evaluation, the onion-bulb pattern in CMT1 is generalized, and not mixed or multifocal as in CIDP.[6]

Paraproteinemic neuropathies are heterogeneous and encompass varied mimickers of typical CIDP **(Table 2)**. IgM paraproteinemic neuropathy with distal acquired demyelinating symmetrical (DADS) phenotype[33] is a sensory-predominant neuropathy characterized by marked ataxia and gait unsteadiness.[34] Myelin-associated glycoprotein (MAG) antibodies are present in about half of IgM-neuropathy patients. IgM-positive DADS neuropathy patients are generally treatment-refractory to standard CIDP immunotherapies.[33,35] While the monoclonal gammopathy in IgM-neuropathy is considered of unclear significance (MGUS), the presence of an IgG or IgA monoclonal gammopathy (especially if it is lambda) and of vascular endothelial growth factor (VEGF) may be associated with an underlying osteosclerotic myeloma, as seen in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)syndrome.[36]

Clinically, POEMS syndrome presents with a severe sensory and motor demyelinating polyradiculoneuropathy, mimicking CIDP. POEMS patients often display systemic symptoms, namely malaise, marked edema, and skin changes. The presence of monoclonal protein, particularly in the setting of thrombocytosis, in a patient with suspected CIDP should prompt screening for POEMS syndrome.[37] Some important additional clinical clues in identifying POEMS Syndrome are that it does not respond to typical CIDP immunotherapy and that patients typically have severe disabling pain, which is rarely found in CIDP. Many POEMS patients are initially diagnosed with CIDP. The EDX findings from POEMS syndrome show more uniform demyelination and axonal degeneration than that seen in CIDP.[38] Nerve biopsies from POEMS patients show more axonal degeneration and neovascularization with fewer onion-bulbs and a similar degree of demyelination than do nerve biopsies from CIDP patients.[39]

6. Sensory and motor axonal polyradiculoneuropathy. In addition to POEMS syndrome, light chain (AL) and transthyretin (TTR) familial amyloid polyneuropathy (FAP) can also present with a sensory and motor axonal-predominant polyradiculoneuropathy.[40,41] Amyloidosis is usually associated with marked dysautonomia (orthostatic hypotension, gastrointestinal dysmotility, and erectile dysfunction), which is rare in CIDP,[16] and produces a rapidly progressive painful neuropathy that is refractory to standard CIDP therapies. Neurolymphomatosis is another condition that may mimic CIDP and should be considered when there is a history of lymphoma (especially non-Hodgkin's), weight loss, and asymmetric course.[42] Finally, diabetic or non-diabetic lumbosacral radiculoplexus neuropathy often presents

as a progressive polyradiculoneuropathy, which may mimic CIDP.[43] Patients usually report severe pain at onset, which is atypical for CIDP. However, a painless diabetic lumbosacral radiculoplexus neuropathy does exist, which often involves all 4 limbs, manifests as a symmetrical axonal polyradiculoneuropathy, and has ischemic features and microvasculitis on nerve biopsy, with the latter finding also seen in painful diabetic and nondiabetic radiculoplexus neuropathy.[44] One may ask how to treat patients with a motor predominant axonal polyradiculoneuropathy that clinically presents like CIDP but does not meet EDX criteria. We believe that such patients should be given immunotherapeutic trials and have a rigorous evaluation after several months. If improvement is seen with quantitative endpoints, treatment should be continued, and if not, then treatment should be discontinued.

Existing therapies: standard of practice & comparative efficacy

Treatment strategies in CIDP aim to achieve remission or to produce meaningful improvement in strength and function. Many patients with CIDP need treatment over very long periods of time, while in others, the disease may go into remission. Irrespective of the therapy used, the dose and frequency of treatment should be appropriate for the severity of neuropathy. For all treatments, the goal should be to produce the most benefit at the smallest dose possible.

Intravenous Immunoglobulins

Current practice recommendations from the EFNS/PNS joint task force advocate the use of the lowest dose of IVIG necessary, with periodic dose reduction.[9] The efficacy of IVIG in CIDP was demonstrated in 1994 in a cross-over study comparing IVIG dosed 0.4g/kg weekly to plasma exchange, with both treatments being beneficial as judged by improvement in the neurological examination (change in neuropathy impairment score).[45] Over time, IVIG efficacy has been established conclusively. A large randomized, multi-center placebo-controlled, cross-over trial (ICE) established the efficacy of IVIG in both the short and long term, using a dosing regimen of 1g/kg every 3 weeks, which helped secure FDA approval.[46] The subsequent randomized, multi-center parallel group IVIG versus intravenous methylprednisolone for CIDP (IMC) trial compared IVIG with intravenous methylprednisolone, and demonstrated comparable efficacy of IVIG to methylprednisolone, using an IVIG dosing regimen of 0.5g/kg per day over 4 days, given monthly for 6 months.[47] A 2013 Cochrane review concluded that IVIG improved CIDP disability for at least 2-6 weeks, with a number needed to treat of 3 (for every 3 CIDP patients treated, one CIDP patient will obtain a positive outcome (or avoid a negative disability outcome)).[48] However, IVIG does not work for all patients with or all subtypes of CIDP. The identification of the IVIG-refractory IgG4 subtype nodopathies, namely neurofascin-155 and contactin-1, exposed the limitations of IVIG in treating certain forms of CIDP. IgG4 does not activate complement well and has low affinity for Fc receptors on effector cells.[49,50]

The topic of optimal IVIG dosing is the focus of ongoing investigation. Of all dosing schedules, the every 3 or 4 week regimens are the most widely used (based on the ICE and IMC

trials) and likely represent the average needs of most CIDP patients. Nevertheless, the most important principle when treating CIDP is that there is no one standard dose that works for all CIDP patients and that dosing should be titrated to individual patients' need and response. Some have advocated an expedited IVIG wean. In such a model, a standard 2g/kg loading dose is given followed by a repeat dose 6 weeks later if the patient does not fully stabilize. Afterwards, the clinician observes for clinical deterioration, and uses this resultant '*time-to-deterioration*' period to guide future infusion frequency.[51] Others have focused on IgG level as a biomarker (the ΔIgG between pre- and post- treatment) to individually-optimize IVIG dosing regimen, and this may help individualize treatment, although it did not correlate with best clinical response for the group.[52-54] Rajabally explored the clinical and economic impacts of varied dosing regimens, and found an individualized dosing regimen to be clinically non-inferior and more cost-effective than a standard dosing regimen.[55] Ongoing studies are exploring 3 different dosing levels (while maintaining frequency at every 3 weeks)[56] as well as reduced-dose, higher-frequency (<14 day) administration.[57,54]

Central to the long-term use of IVIG in CIDP is a review of IVIG pharmacokinetics.[29,58] After intravenous infusion, IgG levels peak immediately and then drop within 2-4 days as IgG enters the extracellular volume space. The half-life of IgG varies from 21 to 30 days. Once IgG enters the intravascular space, its degradation proceeds as a first order process. Key to its breakdown is the saturable endothelial cell receptor FcRn, which protects IgG from endocytosis and lysosomal degradation.[29] Furthermore, a large difference exists in the trough-to-peak

difference in IgG level when comparing infrequent, high-dose IVIG infusions (2g/kg monthly) to more frequent, low-dose subcutaneous IgG infusions (0.5g/kg weekly).[59]

With regards to adverse events, patients may develop headaches, dermatologic eruptions,[60] and more serious thromboembolic events. Caution should be used in patients with coronary artery disease, recent myocardial infarction, stroke, or thrombotic event, hypercoagulability (acquired or familial), oral contraceptive use, and planned travel. In addition, patients with advanced age, preexisting renal compromise, and diabetes are more prone to renal injury. Preventative measures include pre-treatment with antihistamines, corticosteroids, or NSAIDs to mitigate allergic reactions and headaches. One study showed no difference in the likelihood of thromboembolic events as per the average monthly or daily dose of IVIG, but that vascular risk factors should be screened for prior to IVIG commencement.[61] Periodic monitoring of renal function is reasonable. Low-osmolality formulations should be pursued when possible as sucrose is a major aggravator of renal injury and glucose of hyperglycemia.

Subcutaneous Immunoglobulin

In light of the established efficacy of intravenous IVIG,[46,48] the question arose as to whether immunoglobulin could be delivered in a more convenient fashion with less adverse events. Subcutaneous immunoglobulin (SCIG) emerged as a potential alternative to IVIG. A large, international, randomized, placebo-controlled trial confirmed both the efficacy and tolerability of SCIG.[62] Patients in the once-weekly high dose (0.4g/kg) and low dose (0.2g/kg)

SCIG groups performed better than placebo, although there was no significant difference between high and low-dose groups. As compared to IVIG, the overall adverse event profile of SCIG was favorable.

The major challenge with SCIG is skin irritation, which is dose-dependent, but also seems to lessen with time.[63] It is safe and reasonable to consider switching from IVIG to SCIG for convenience, poor IV access, end-of-dose wear off effect, or adverse events with IV infusions.[64] However, prior to switching, patients must be stable on IVIG, as there is currently insufficient evidence for SCIG as inductive therapy in treatment-naïve CIDP patients.

Corticosteroids

While corticosteroids (CCS) represent another class of effective therapy, the primary concern is adverse events, especially with prolonged therapy. One of the first trials to demonstrate the efficacy of prednisone was conducted in 1982 by Dyck and colleagues, using a high dose (120mg) alternate day regimen for 3 months.[65] Although patients may experience improvement soon after starting treatment, attaining maximal response can take on average 3 to 6 months.[66,67] A well-planned tapering regimen is particularly important. Similar to IVIG, tapering is usually started after the patient stops improving and reaches a plateau. CCS can be tapered by decreasing the daily dose by 5-10 mg every 1-4 weeks, or by transitioning to an alternate day regimen.

Other CCS formulations beyond oral prednisone have also been explored. Investigators studied the efficacy and tolerability of pulsed monthly dexamethasone, administered orally 4 days per month at 40mg per day, versus daily standard prednisolone dosing. The dexamethasone arm showed a median time to remission of 20 weeks (as compared to 39 weeks), less deterioration after discontinuation, and less insomnia and Cushingoid features.[67] A single-center retrospective study explored the utility of pulsed CCS in the form of intravenous methylprednisolone (IVMP) as compared to daily oral prednisone and IVIG.[68] The most common dosing regimen for the IVMP arm was an induction dose of 1g daily for 3-5 days followed by 1gm once a week, tapered in frequency and dose. IVMP patients had less weight gain and Cushingoid features as compared to those on oral daily prednisone, with a higher response rate also seen in the intravenous arm at 6 months.

Comparison of IVIG and CCS is another area of focus. The IMC trial discussed earlier was a prospective 6-month European trial that further explored the efficacy and tolerability of IVMP, administered monthly in the form of 0.5g daily for 4 days, as compared with IVIG administered monthly in the form of 0.5g/kg daily for 4 days. Patients randomized to the IVIG arm showed faster remission and better compliance, with less adverse events. However, the IVMP arm had longer median disease remission (14 months) after drug discontinuation as compared to IVIG (4.5 months). In addition, a greater percentage of patients in the IVMP arm remained in remission at 6 months. Whether this holds true for longer follow-up remains to be seen. Finally, a retrospective study comparing characteristics between patients who could be

withdrawn from treatment (treatment withdrawal group) and those that could not (treatment dependent), found that the treatment-dependent group responded more frequently to IVIG, showed CCS treatment-resistance, and presented more commonly with a multifocal deficit. Successful treatment withdrawal occurred more often with CCS, however.[69]

Given the improved long-term remission profile with IVMP, some have explored whether there is a role for combined IVMP and IVIG therapy from disease onset. To answer this question, a prospective trial (OPTIC) is underway, randomizing patients to either 1g/kg IVIG every-3-week dosing + 1gm IVMP every-3-week dosing *or* 1g/kg every-3-week IVIG dosing + placebo, over a course of 18 weeks.[70]

In addition to the adverse events discussed above, CCS carry numerous other risks, such as hyperglycemia, CCS-induced diabetes, osteopenia, infection, and gastritis, among many others, and which need to be discussed and addressed fully with patients from the start, but which are beyond the focus of this review, and which are summarized in guidelines.[71]

Plasma Exchange

Plasma exchange (PE) is an effective therapy for treatment-refractory cases of CIDP, namely those that have not responded to IVIG or CCS. Furthermore, PE remains a useful alternative for patients unable to receive IVIG or CCS due to adverse event risk or contraindications. PE is postulated to remove circulating immunoglobulins, complement, cytokines, and antibodies. Data from a prospective, double-blind, sham-controlled trial in 1986

showed improvement in combined measures of nerve conduction as well as the Neuropathy Impairment Score (NIS) by week 3 in the PE group as compared to sham.[72] A crossover, sham-controlled prospective trial conducted 10 years later re-demonstrated the benefit of PE after 10 exchanges, with improvements noted in mean NIS scores, grip strength, clinical disability grade, and summated mean motor potential amplitudes and conduction velocities.[73] A 1994 crossover, prospective, observer-controlled study comparing PE to IVIG showed that both immunotherapies produced large degrees of neurological improvement as graded by the NIS and the summated compound muscle action potentials.[45] The authors concluded that, while both treatments were equally effective, IVIG might be preferable due to its ease of use.

PE is most often used initially in severely disabled patients, in patients refractory to CCS or IVIG, or as rescue therapy during CIDP exacerbations. Data regarding the efficacy of PE as a long-term treatment option for CIDP is limited. Of note, within weeks to months after completion of treatment, up to 50-67% of patients deteriorate. However, all three primary treatments of CIDP (CCS, IVIG and PE) require ongoing use and cannot be given for a short time and then abruptly stopped without worsening of disease. PE can, however, sometimes be used intermittently either alone or as adjunctive therapy with CCS in the outpatient setting.

Adverse event considerations include fluid overload, especially in those with congestive heart failure, liver disease, and renal disease, as well as infection risk. ACE-inhibitors should be held 24h prior to exchange.[74]

Treatment failure and ongoing trials

Despite the efficacy of IVIG, SCIG, CCS, and PE in the treatment of CIDP, some patients do not respond to any of these modalities. When lack of treatment response occurs, the first step is to confirm that the patient actually has CIDP. In our experience, if a patient has a rapidly progressing, ongoing demyelinating polyradiculoneuropathy that has not responded to conventional immunotherapy, the most likely explanation is a disease mimicker, most commonly POEMS syndrome, for which repeat immunofixation electrophoresis and VEGF levels should be obtained. Other possible reasons for poor treatment response include an IgM DADS subtype of CIDP or the nodopathy subtypes (NF-155 and contactin-1). If the case is indeed treatment-refractory typical CIDP, combined PE and CCS or IVIG and CCS can be tried. In addition, patients with antibodies to neurofascin-155 are refractory to IVIG but are quite sensitive to rituximab and probably PE,[75] while those with antibodies to contactin-1 respond better to CCS than IVIG.[76] Irrespective of antibody status, rituximab appears to be a promising therapy even for antibody-negative, treatment-refractory CIDP, although not all patients respond.[75] Roux et al evaluated 28 antibody-negative CIDP patients and demonstrated that 75% of patients improved, although patients had concomitant hematologic disorders or autoimmune disease.[77] Median time to improvement was 6 months and only 2 patients required re-treatment by 2-year follow up. Querol examined contactin-1 and neurofascin-155 positive, treatment-refractory CIDP patients receiving rituximab, and demonstrated clinical improvement and decline in antibody titers. An ongoing Japanese randomized controlled trial is evaluating the efficacy and safety of rituximab

in CIDP patients with and without anti-paranodal antibodies (NCT03864185). High-dose pulsed cyclophosphamide also shows improvement in muscle strength, functional status, and EDX parameters in treatment-refractory CIDP, but potential side effects need to be carefully discussed with patients.[78-80]

Data regarding the role of other immunosuppressants is limited to case series, anecdotal experience, or mixed evidence at best.[81] For example, azathioprine combined with prednisone was not found to be superior to prednisone alone in one trial, although the study was limited by short duration.[82] Two placebo-controlled randomized trials found fingolimod[83] and low dose methotrexate[84] to not be efficacious in CIDP. Ongoing trials are evaluating the role of therapies targeting the neonatal Fc receptor (FcRn) (NCT04051944, NCT04281472).

Outcome measures

CIDP is a heterogeneous disorder with marked variability in treatment response.[29] With effective treatment, long term disability is generally limited, while poor outcome is tied to delay of therapy.[85] An ongoing multi-center prospective study aims to better define the natural history of CIDP.[86] As CIDP currently has no established biomarkers, measurements of neuropathy severity are needed, not only for diagnosis, but also to monitor treatment response.

The NIS (previously called the Neurologic Disability Score) was among the first outcome measures used to establish IVIG and PE efficacy in CIDP.[45,72,87] The NIS is a summed score of a standard representative list of motor, sensory, and muscle stretch reflex impairments, which

provides a robust quantification of the standard neuropathy exam to allow for objective visit-to-visit surveillance of treatment response. In a prospective, semi-blinded, and standardized assessment of CIDP patients, investigators found the NIS as well as the NIS-weakness subscore to scale with neuropathy abnormality.[88] In addition, the summated CMAP score (a sum of the CMAP of the ulnar, fibular, and tibial motor nerves) scaled with neuropathy abnormality and also correlated with the NIS. The NIS has evolved over time to apply to different types of neuropathy, including diabetic polyneuropathy, CIDP, and recently transthyretin amyloidosis neuropathy.[89]

Over the last decade, renewed interest has focused on capturing clinical outcome using multiple modalities for research trials in CIDP. A combined set of outcome measures for CIDP trials and clinical evaluation emerged, incorporating assessment of (1) *disability* (The Inflammatory-Rasch Built Overall Disability Scale (I-RODS), The Inflammatory Neuropathy Cause and Treatment (INCAT)); (2) *strength* (grip strength testing, manual muscle testing, Medical Research Council Summated Score); (3) *gait assessment* (timed up and go); and (4) *quality of life measures* (EuroQoL-5 Dimension Questionnaire, Patient Global Impression of Change).[90,91] While this approach applies to research trials, it is equally important in the clinical setting.

Of such measures, three warrant particular attention, namely grip strength, the I-RODS, and the INCAT. Grip strength, performed using either a Jamar or Vigorometer device, is a well-validated and quick measure of impairment.[90] It provides objective evidence of global neurologic

status and correlates well with the I-RODS score.[92] In a Dutch study of 14 patients with CIDP, grip strength correlated with IgG levels one week after IVIG infusion, thus allowing individualization of IVIG dosing, given the notable inter-patient variability in IVIG pharmacokinetics.[93] The I-RODS is a validated and disease-specific outcome measure for CIDP patients that is widely used.[94] The INCAT is another widely used primary outcome measure for CIDP trials,[66] although it is not without its limitations, such as disproportionate item weighting, insensitivity to minor changes, and inability to capture activity limitation from proximal arm weakness.[95] Important in the discussion of CIDP outcome measures is the concept of minimal clinically improvement difference (MCID), which was used to validate the efficacy of the ICE trial.[96] The MCID is, '*the smallest difference in score in the domain of interest which patients perceive as beneficial*.'[97]

How we treat CIDP

While there is no uniformly agreed-to approach to the long-term treatment of CIDP, we conclude with a review of how we approach CIDP. Our approach is not definitive and other approaches should be given equal, if not more, consideration. We only share an approach that we have found over the years to be effective and practical.

Unless there is a contraindication, our first-line treatment is IVIG. As discussed earlier, there is no set IVIG dose or frequency for all CIDP patients. Dosing always depends on the individual patient. Severely affected, rapidly-progressive patients require higher IVIG doses

than milder, slowly-progressive cases. As discussed earlier, many experts advocate an every 3 or 4 week dosing schedule. However, some patients require more frequent dosing, while others less. The concept of response-based immunotherapy should guide the long term treatment of CIDP.[88] Thus, dosing should be titrated to individual patient need. Periodic and frequent assessment by a trained neuromuscular physician using validated outcome measures allows for individualization of dosing and proper and timely weaning of immunotherapy in CIDP patients over long-term follow-up.

On the basis of data from the early IVIG CIDP studies as well as more recent data on immunotherapy and SCIG dosing,[45,59,62,88] we usually start, in more severe cases, by loading with 2g/kg over 5 days and then initiate 0.4g/kg weekly. In milder cases, a loading dose may not be necessary, and we may begin with IVIG 0.4 g/kg weekly for 4 weeks and then every 2 weeks thereafter. In more severe cases, 0.4 g/kg twice a week is sometimes given. We maintain the patient on the same dose until s/he stops improving and reaches plateau. The goal is not to get the patient's neurological examination back to normal but to substantially improve the patient's clinical examination as well as strength and function. We see the patient back in 3-month intervals unless there is rapid worsening, in which case we see them more frequently. Once plateau is achieved, we start a slow taper by increasing the interval between IVIG doses, typically every 3 months. There is no clear guidance on how fast the taper should be, but in most patients, we attempt to completely taper off treatment at some stage. Patients may successfully discontinue treatment and remain in remission, or continue to require a variable dose of IVIG

ranging from once a week to once every six weeks. Therefore, the treatment is tailored on a case by case basis.

To reiterate, we only discuss herein the approach that we have found helpful in our centers' clinical experience. We encourage readers to refer to other IVIG dosing algorithms as discussed in the IVIG section earlier.

Depending on disease severity at presentation, we may add IVMP to IVIG, fully cognizant that formal data is still lacking in this regards, although the OPTIC data does show some early promise.[70] We use a maintenance dose of 1g IVMP weekly, typically coinciding with the weekly 0.4g/kg IVIG infusions. However, we wean IVMP faster, due to its adverse event profile. Although daily or alternate-day oral prednisone is efficacious, we prefer to avoid it whenever possible given its heightened adverse event profile. However, it is an excellent option in patients with no venous access or poor tolerance to IVIG.

In cases of suboptimal response to IVIG and/or CCS, changing the treatment to PE can be considered. PE remains the first-line treatment in patients who are rapidly worsening. PE can be a temporary treatment until another effective treatment is be found. However, the authors have had CIDP patients in whom CCS and IVIG do not work but PE does. We also combine PE with CCS in such treatment-refractory patients if needed. In these patients, long-term PE is very effective, although it does present long-term challenges with venous access and infections.

In cases refractory to standard treatment, the first step is to re-visit the diagnosis of CIDP. Depending on the clinical phenotype, we repeat a thorough evaluation as delineated in **Table 1**.

A nerve biopsy may be needed. In patients with antibodies to neurofascin-155 and contactin-1, rituximab should be considered. Rituximab or cyclophosphamide can also be considered in seronegative patients if no alternative etiology is identified, or in patients who respond to PE, although therapeutic efficacy data is still quite limited.

Conclusion

The diagnosis of CIDP remains primarily clinical, supported by demonstrating demyelination on EDX testing following standardized criteria such as those of the EFNS/PNS. In some cases, CSF studies, MR or US imaging, and nerve pathology are helpful. Response to immunotherapy should be determined based on objective measures. There is an ongoing need for diagnostic and therapeutic biomarkers, as well as alternative treatment options for patients who do not respond or cannot tolerate currently available agents.

Figure 1:

Inflammation and onion-bulbs (OB) seen in transverse paraffin sections from 2 patients with CIDP. Serial sections stained with (A) hematoxylin–eosin and (B) CD45 show a perivascular endoneurial collection of inflammatory cells and background OB in a patient with CIDP. Three consecutive paraffin cross-sections show: (C) hematoxylin-eosin stain a large inflammatory collection in epineurium adjacent to the perineurium that (D) carries antibody to T cells (CD3) and (E) OB are confirmed by their reactivity to a Schwann-cell preparation (S-100). Inflammatory infiltrates are more common in acquired neuropathies.[6]

Figure 2:

Mixed onion-bulbs (OB) seen in nerve biopsy epoxy sections stained with methylene blue, showing OB surrounding some fibers, whereas other myelinated fibers do not have OB, as seen in (A) CIDP (acquired) with biopsy from nerve root; (B) CIDP (acquired); and (C) focal hypertrophic neuropathy of the median nerve (focal CIDP, acquired). The mixed pattern is found much more commonly in acquired neuropathies.[6]

Abbreviations

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDX, electrodiagnostic; EFNS/PNS, European Federation of Neurological Society / Peripheral Nerve Society; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; CCS, corticosteroids; PE, plasma exchange; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; GBS, Guillain Barre Syndrome; A-CIDP, acute onset CIDP; SIDP, subacute inflammatory demyelinating

polyneuropathy; CMT, Charcot Marie Tooth; DADS, distal acquired demyelinating sensorimotor neuropathy; MAG, myelin-associated glycoprotein; POEMS, Polyneuropathy Organomegaly Endocrinopathy M-protein and Skin changes; MGUS, monoclonal gammopathy of unknown significance; AL, acquired light chain; TTR, transthyretin; IVMP, intravenous methylprednisolone; NIS, neuropathy impairment score; I-RODS, Inflammatory-Rasch Built Overall Disability Scale; INCAT, Inflammatory Neuropathy Cause and Treatment;

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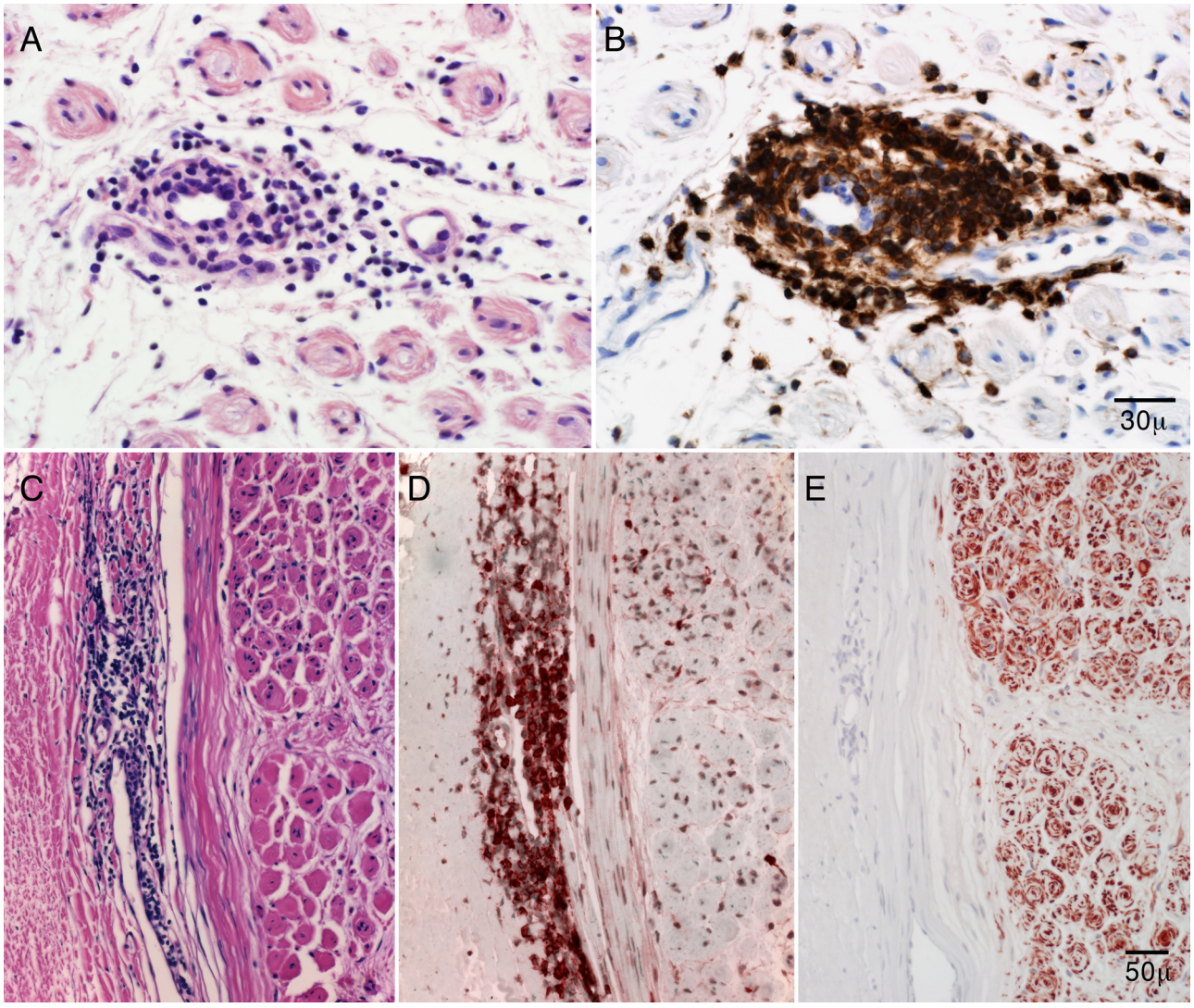

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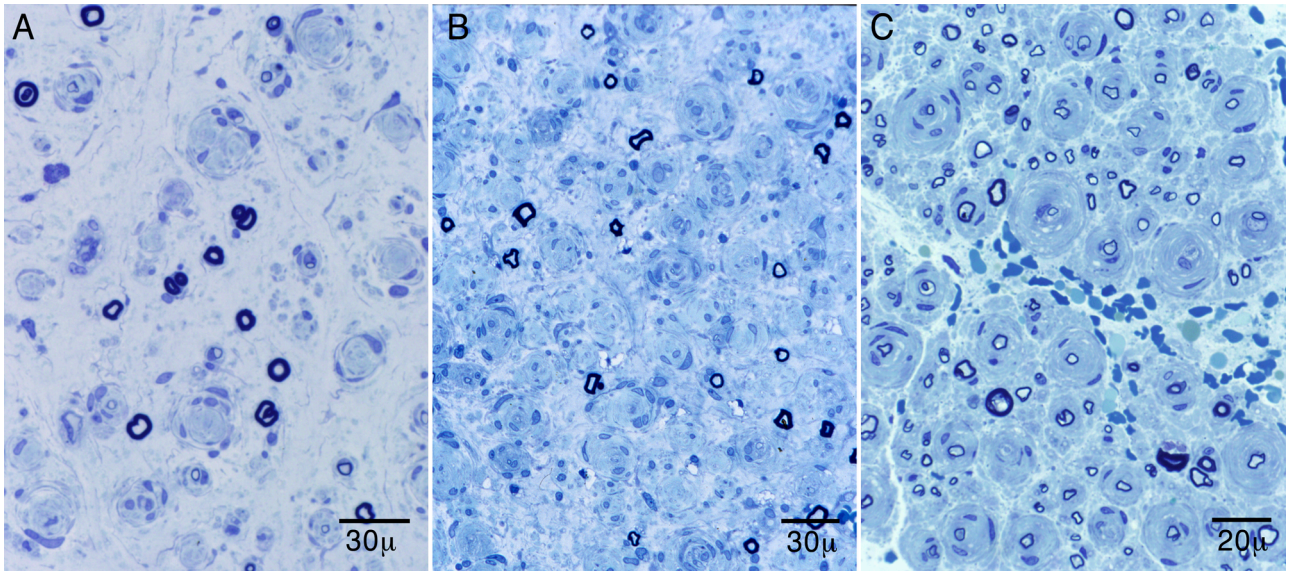

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Table 1. Potentially useful lab tests in the evaluation of CIDP variants and mimickers

Clinical presentations of CIDP variants or disease mimickers	***Potentially helpful laboratory tests***
Length-dependent sensory greater than motor, axonal predominant peripheral neuropathy	HbA1c, vitamin B12, methylmalonic acid, copper, zinc, ceruloplasmin, TSH.
Non length-dependent sensory ganglionopathy/neuronopathy	SSA and SSB antibodies, minor salivary gland biopsy, Anti-Hu, anti-CRMP antibodies, MR imaging of nerve roots, somatosensory evoked potentials, CSF evaluation
Upper limb predominant	GM1 and disulphated heparin disaccharide (NS6S) antibodies (MMN), complete blood count, sedimentation rate, C-reactive protein, ANCA profile, ANA, extractable nuclear antigen profile, chronic hepatitis screen, nerve biopsy, genetic testing (PMP22 if HNPP suspected)
Sensory and motor demyelinating neuropathy	Genetic testing (PMP22), Complete blood count, monoclonal protein screen, Myelin-Associated Glycoprotein antibodies, VEGF level, skeletal survey
Sensory and motor axonal polyradiculoneuropathy	Monoclonal protein screen, serum free light chains, NT-proBNP, fat aspirate. Genetic testing (TTR), ^{99m}Tc-PYP scan (TTR)

HbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; CRMP, collapsin response mediator protein; MR, magnetic resonance; CSF, cerebrospinal fluid; MMN, multifocal motor neuropathy; ANCA, anti-neutrophil cytoplasmic antibodies; ANA, antinuclear antigen; PMP22, peripheral myelin protein 22; HNPP, hereditary neuropathy with liability to pressure palsy; VEGF, vascular endothelial growth factor, AL, acquired light-chain; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; TTR, transthyretin; ^{99m}Tc-PYP scan, 99mTechnetium-Pyrophosphate

Table 2. Paraproteinemic neuropathy disease mimickers of CIDP.

Monoclonal gammopathy subtype	**Plasma cell disorder**	**Peripheral neuropathy phenotype**	**Autonomic involvement**	**Systemic symptoms**	**Helpful laboratory markers**
IgM kappa or lambda	MGUS	Length-dependent, sensory predominant, demyelinating	-	-	Myelin-Associated Glycoprotein (MAG) antibodies
	Waldenström Macroglobulene-mia	Similar to IgM-MGUS neuropathy with more common axonal involvement	-	Yes	Hemoglobin, platelet count, IgM levels, β2-microglobulin
IgA or IgG, lambda	POEMS syndrome	Sensory and motor, demyelinating more than axonal, polyradiculoneuropathy	+	Yes	Platelet count (thrombocytosis, VEGF, endocrine studies
Any type including light chain only	AL Amyloidosis	Length-dependent (or polyradiculoneuropathy) sensory and motor, axonal	+++	Yes (patients look the sickest)	24-hr urine total protein, complete blood count, creatinine, alkaline phosphatase, troponin, brain natriuretic peptide, or N-

					terminal pro-BNP levels.

EDX, electrodiagnostic; MGUS: monoclonal gammopathy of undetermined significance; MAG, myelin associated glycoprotein; DADS, distal acquired demyelinating sensorimotor neuropathy; NCS, nerve conduction studies; VEGF, vascular endothelial growth factor; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and skin changes; AL Amyloidosis, acquired light chain amyloidosis; N-terminal proBNP, N-terminal prohormone brain natriuretic peptide